

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40-274

BIOEQUIVALENCE

Hydroxychloroquine Sulfate
200 mg Tablets
ANDA #40-274
Reviewer: Moheb H. Makary
WP 40-274SD 897

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date;
August 28, 1997

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

The objective of this study was to compare the blood levels of Hydroxychloroquine, after administration of a single 200 mg dose of Hydroxychloroquine Sulfate 200 mg Tablet (Mylan Pharmaceuticals Inc.) to Plaquenil[®] 200 mg tablet (Sanofi Winthrop) under fasting conditions. The firm has submitted comparative dissolution profiles for its Hydroxychloroquine Sulfate 200 mg Tablets versus Plaquenil[®] 200 mg Tablets. The formulation for the drug product Hydroxychloroquine Sulfate 200 mg Tablets was also submitted.

II. Background:

Hydroxychloroquine is indicated for the suppressive treatment and treatment of acute attacks of malaria due to Plasmodium vivax, P. malariae, P. ovale, and susceptible strains of P. falciparum. It is also indicated for the treatment of discoid and systematic lupus erythematosus and rheumatoid arthritis. Use of this drug is contraindicated in the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound.

The amount of information in literature on the pharmacokinetics of hydroxychloroquine is scarce. According to the data available in the Agency, an oral dose of a 200 mg tablet resulted in a C_{max} in whole blood of 120-170 ng/mL and a T_{max} of 3-4 hours. Terminal half-life ranged 19-28 days. It was suggested that whole blood concentrations of hydroxychloroquine rather than its plasma concentrations be measured in pharmacokinetic studies. The peak metabolite concentrations were about 1 to 5% of the peak hydroxychloroquine blood concentrations. The clinical implication and toxicity of the metabolites have not been established. The study also showed no evidence of nonlinear elimination or distribution process of hydroxychloroquine. It was reported that a mean bioavailability of 74% for an oral administration of a tablet.

Dosage and administration are dependent on the indications. Hydroxychloroquine sulfate is currently available in 200 mg film coated tablet for oral administration as Plaquenil[®] Sulfate Tablets by Sanofi Winthrop.

III. Study #HYDR-9650 for Single-Dose of Hydroxychloroquine Sulfate, 200 mg Tablet, Under Fasting Conditions:

Study site: PRACS Institute, Ltd.
Fargo, ND.
Medical Investigator:
Bruce L. Dahl, M.D.

Analytical site:

Study design: Open label, randomized, two-treatment, single-dose, parallel bioequivalence study, under fasting conditions. Subjects were dosed in one group.

Subjects: Eighty (80) male subjects were accepted for entry into the clinical portion of the study. Seventy-nine (79) subjects successfully completed the clinical portion of the study. Subjects were dosed in one group.

Selection criteria: The subjects were between 18 to 50 years of age. All subjects were within $\pm 10\%$ of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination and laboratory evaluation. The subjects had no history of significant chronic diseases, hepatitis or drug/alcohol abuse. Subjects who were considered ineligible for the study if they had abnormal laboratory test results; donated more than 450 mL of blood or plasma within 28 days prior to the initial dose of study medication; use of any medication within the last 14 days prior to the initial dose of study medication; had consumed vitamins, alcohol, caffeine-or

xanthine-containing foods or beverages within 48 hours prior to study medication; history of or abnormally low glucose-6-phosphate dehydrogenase laboratory test; detection of urine porphyrins; ingestion of any quinine-containing medications or beverages; had participated in any other drug study 30 days prior to study medication.

Dose and

Treatments:

Treatment A: 1x200 mg Plaquenil[®] Tablet (Sanofi Winthrop), lot #B27ONE, Exp. 5/98, potency 97.9%, content uniformity 97.9% (CV=2.8%), administered following an overnight fast.

Treatment B: 1x200 mg Hydroxychloroquine Sulfate Tablet (Mylan), lot #2C001M, batch size 150,000 Tablets, potency 98.5%, content uniformity 99.1% (CV=1.2%), administered following an overnight fast.

Food and fluid
intake:

Subjects fasted for ten hours prior to dosing. Lunch was served five hours after dosing. Dinner was served ten hours after dosing.

Blood samples:

Ten mL (10) blood samples were collected at 0 (pre-dose) 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 312, 480, 648, 816, 984, 1152, 1320, 1488 and 1656 hours after dosing. Whole blood was extracted and stored in labeled tubes at -20°C or lower until analysis.

Assay Methodology:

Determination of hydroxychloroquine concentrations in whole blood were performed by

Sensitivity: The limit of quantitation was 1 ng/mL for hydroxychloroquine.

Linearity: The assay was linear over the concentration

range of 1 to 350 ng/mL for hydroxychloroquine.

Assay specificity: Specificity was accomplished by evaluating 6 sources of heparinized whole blood and injecting several OTC drug standards on the HPLC to establish noninterference with hydroxychloroquine and internal standard. There were no interferences with hydroxychloroquine or the internal standard.

Recovery: The recovery was 84.0% for hydroxychloroquine and was 87.3% for the internal standard.

Interday precision: The between-batch coefficients of variation ranged from 1.99% to 9.09% and within-batch ranged from 1.72% to 7.92% for hydroxychloroquine.

Stability: Freeze-Thaw Stability: Hydroxychloroquine was spiked into whole blood at low and high concentrations. These samples were subjected to three freeze-thaw cycles. Hydroxychloroquine samples were found to be stable through three freeze/thaw cycles. Processed sample stability: processed (extracted) samples were set at room temperature up to 4 hours. The samples did not show significant degradation when stored at room temperature up to 4 hours. Long term stability: stability was assessed by quantitation of spiked whole blood samples which were frozen at -70°C and stored for 44 days. The spiked samples contained 200 ng/mL and 3 ng/mL hydroxychloroquine. The results showed no significant degradation of hydroxychloroquine for a period up to 44 days.

Statistical Analysis:

Statistical analysis was performed on hydroxychloroquine data using SAS. Analysis of variance was performed using the GLM procedure. The two one-sided tests were used to estimate the 90% confidence intervals for the pharmacokinetics parameters.

IV. In Vivo Results:

Eighty (80) normal, healthy subjects were recruited for the study and seventy-nine (79) successfully completed the clinical portion of the study. Subjects were dosed in one group. Subject #65 elected to undergo surgical repair of a left inguinal hernia and was dropped from the study participation. One hundred forty-nine adverse events were reported in forty-one of the eighty subjects dosed over the course of the study. Of the one hundred forty-nine reported adverse events, twenty-three were probably or possibly related to study drug. In the opinion of the investigators, the other one hundred twenty-six adverse events were either remotely related to or unrelated to study drug. None of the adverse events were considered serious.

The plasma concentrations and pharmacokinetics parameters for hydroxychloroquine are summarized in Table I.

Table I

Mean Hydroxychloroquine Blood Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg Hydroxychloroquine Sulfate (1x200 mg Tablet) under Fasting Conditions
(N=79)

	<u>Treatment A</u>	<u>Treatment B</u>
	Reference	Mylan-Test
	Lot #B270NE	Lot #2C001M
	ng/mL (CV)	ng/mL (CV)
<u>Time</u>		
hr		
0	0	0
0.5	30.9 (86)	30.5 (83)
1	61.9 (68)	58.4 (58)
1.5	83.4 (60)	75.9 (44)
2	93.7 (48)	88.2 (34)
2.5	99.1 (43)	95.2 (32)
3	100.6 (42)	94.0 (27)
3.5	99.9 (38)	93.7 (27)
4	98.2 (36)	91.5 (27)
5	94.0 (34)	86.2 (26)
6	100.8 (31)	93.3 (24)
8	90.1 (29)	82.6 (25)

10	72.7 (29)	67.0 (26)
12	62.4 (27)	57.4 (25)
24	34.7 (27)	31.7 (25)
36	27.9 (26)	26.5 (24)
48	23.4 (27)	21.2 (25)
72	18.6 (25)	17.2 (26)
96	16.9 (27)	15.3 (26)
120	14.8 (28)	14.1 (27)
144	13.7 (28)	12.9 (26)
312	9.0 (28)	8.5 (26)
480	6.5 (31)	6.4 (30)
648	5.0 (30)	5.0 (34)
816	3.9 (25)	3.9 (27)
984	3.1 (26)	3.2 (29)
1152	2.6 (32)	2.5 (36)
1320	2.0 (33)	2.2 (37)
1488	1.7 (47)	1.7 (46)
1656	1.2 (69)	1.4 (48)

AUC(0-t) (ng.hr/mL)	10768.4 (26)	10382.0 (25)
AUCINF (ng.hr/mL)	12015.0 (25)	11855.1 (23)
Cpeak (ng/mL)	117.4 (34)	108.1 (24)
Tpeak (hr)	3.80	3.37
Kel (1/hr)	0.0013	0.0012
T1/2 (hr)	564.0	620.0

90% CI

LnAUC(0-t)	87.8-106.3%
LnAUCI	90.1-108.6%
LnCpeak	84.7-106.4%

1. For hydroxychloroquine, the least squares means for AUC(0-t), AUCI and Cpeak values were 3.6%, 1.3% and 7.9% lower, respectively, for the test product than for the reference product. The differences were not statistically significant and the 90% confidence intervals for the above parameters were within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The hydroxychloroquine blood levels peaked at 2.5 and 6 hours for the test and the reference products, respectively, following their administration under fasting conditions.

V. Formulation:

Mylan's formulation for its Hydroxychloroquine Sulfate 200 mg Tablets is shown in Table II.

VI. In vitro Dissolution Testing: (USP Method)

Method: USP 23 apparatus II (paddle) at 50 rpm

Medium: 900 mL of water

Sample Times: 15, 30, 45 and 60 minutes

Number of

Tablets: 12

Test Product: Mylan's Hydroxychloroquine Sulfate Tablets, 200 mg
Lot #2C001M

Reference

Product: Sanofi Winthrop's Plaquenil[®] Tablet, 200 mg
lot #B27ONE

Specification:

The dissolution testing results are presented in Table III.

VII. Comments:

1. The firm's single-dose bioequivalence study #HYDR-9650 under fasting conditions, conducted on its 200 mg hydroxychloroquine sulfate tablets is acceptable. The two study drugs did not differ significantly with respect to mean values for any of the pharmacokinetics parameters. The 90% confidence intervals for $\text{LnAUC}(0-t)$, LnAUCinf and LnCpeak are within the acceptable range of 80-125% for hydroxychloroquine.

2. The in vitro dissolution testing for the test product 200 mg hydroxychloroquine sulfate tablets is acceptable.

VIII. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Mylan Pharmaceuticals Inc., on its Hydroxychloroquine Sulfate 200 mg Tablet, lot #2C001M, comparing it to Plaquenil[®] 200 mg Tablet manufactured by Sanofi Winthrop, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Hydroxychloroquine Sulfate Tablet, 200 mg is bioequivalent to the reference product, Plaquenil[®] 200 mg Tablet manufactured by Sanofi Winthrop.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its Hydroxychloroquine Sulfate 200 mg Tablets, lot

#2C001M, comparing it with the Sanofi Winthrop's Plaquenil[®] 200 mg Tablets is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

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The firm should be informed of the above recommendations.

Table III. In Vitro Dissolution Testing						
Drug (Generic Name): Hydroxychloroquine Sulfate Dose Strength: 200 mg ANDA No.: 40-274 Firm: Mylan Submission Date: August 28, 1997 File Name: 40274SD.897						
I. Conditions for Dissolution Testing:						
USP 23 Basket: Paddle: X RPM: 50 No. Units Tested: 12 Medium: 900 mL of water Specifications: Reference Drug: Plaquenil Assay Methodology:						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #2C001M Strength(mg) 200			Reference Product Lot # B27ONE Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
15	57		16.2	32		7.0
30	86		10.1	55		6.6
45	92		4.4	71		7.1
60	94		2.9	81		5.4

CC:

Endorsements: *Moheb H. Makary*
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE *Rama P. M. Mhatre* Date: *1/2/98*

Concur: *PS* Date: *1/5/98*
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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BIOEQUIVALENCY - ACCEPTABLE

- | | | |
|----|--------------------------------------|------------------------------------|
| 1. | FASTING STUDY (STF) | Strengths: <u>200mg</u> ACCEPTABLE |
| | Clinical: <u>PRACS Institute Ltd</u> | Outcome: AC IC UN NC |
| | Analytical: _ | |
| 2. | DISSOLUTION DATA (DIS) | All Strengths ACCEPTABLE |
| | | Outcome: AC IC UN NC |

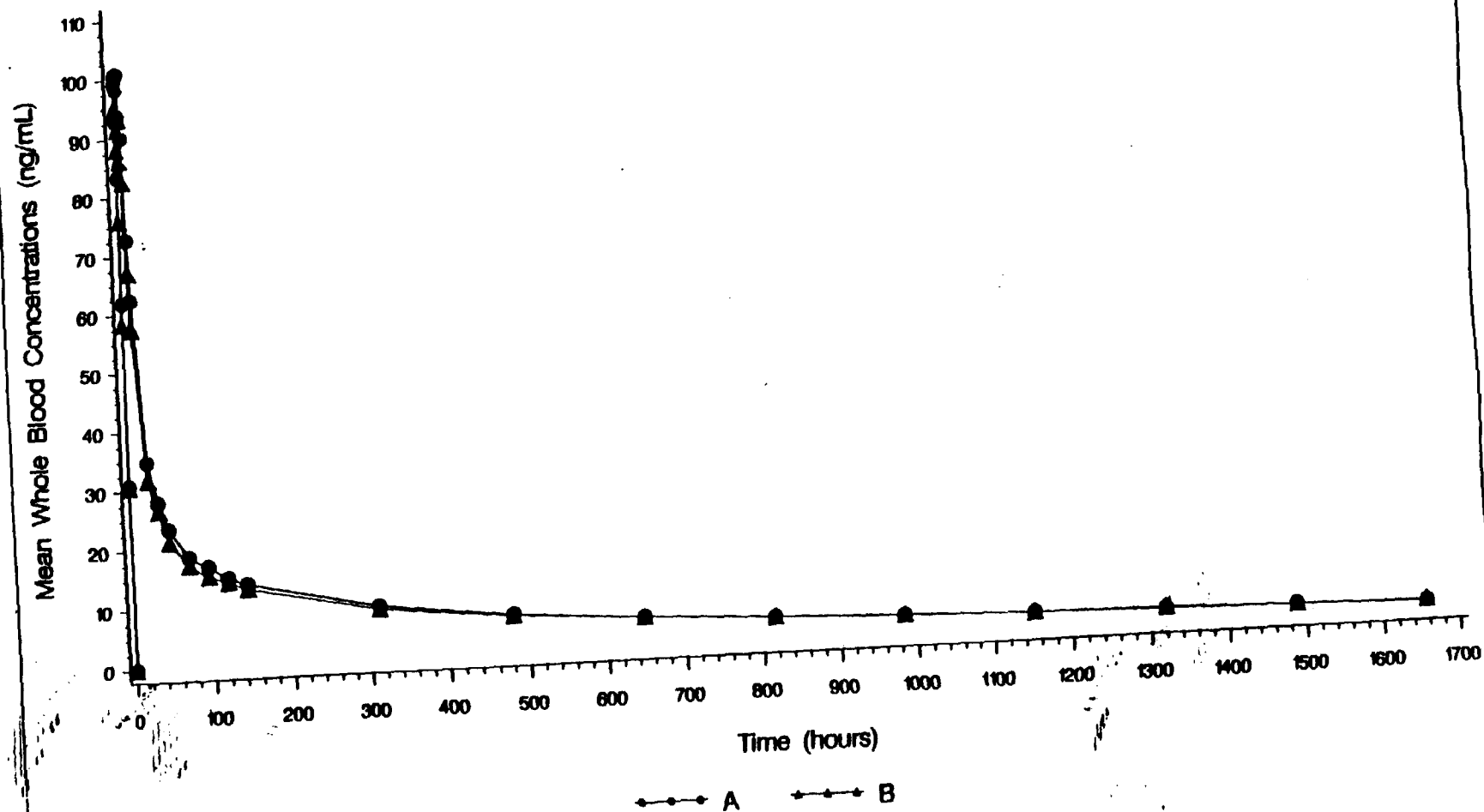
OUTCOME DECISIONS: ACCEPTABLE

AC - Acceptable
NC - No Action

UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

Hydroxychloroquine (HYDR-9650)
Total Dose: 200 mg (1x200mg Tablets), Study Type: Fasting
Mean Hydroxychloroquine Whole Blood Concentrations
N=79



Treatment A is A (Plaquenil)
Treatment B is B (Hydroxychloroquine)